Rev. R. Acad. Med. Catalunya, 2019; 152-161

Ingrés d'Acadèmics d'Honor

PERSONALISED MEDICINE – BETWEEN HYPE AND HOPE. ITS PRESENT ROLE IN ATRIAL FIBRILLATION

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Based on the lecture held on the occasion of the Recepció de l`Acadèmic d`Honor on November 26, 2019

KEY WORDS: Atrial fibrillation; risk prediction; prognosis; artificial intelligence.

The electrocardiogram although more than 100 years old since its introduction by Einthoven, is still the most important clinical tool to personalise the management of atrial fibrillation (AF). The ECG as a non-invasive, well-standardized, and cost-effective diagnostic tool that informs not only about the type of heart rhythm but also about the presence of concomitant heart disease.

The prevalence and incidence of AF are steadily increasing. Based on claims data from 8.2 million insured subjects, we predicted its prevalence in the German population to increase from 2.132 % in 2009 to 2.661 % in 2020 (Th Wilke, et al., 2013). This increase in the prevalence and incidence of AF is a world-wide phenomenon (SS Chugh, et al., 2014).

ATRIAL FIBRILLATION IS NOT JUST AN ELECTROCARDIOGRAPHIC DIAGNOSIS BUT A COMPLEX DISEASE OFTEN ASSOCIATED WITH CO-MORBIDITIES AND WITH SEVERE SEQUELAE.

The list of risk factors and markers for occurrence, progression, and complications of AF is long (P Kirchhof, et al. 2012; G Breithardt, et al., 2012). Rarely, AF may have a strong monogenetic background (as first demonstrated by R Brugada et al., 1997). Almost all common cases have an acquired background. In the Atherosclerosis Risk in Communities (ARIC) Study, 57 % of new cases of AF could be attributed to elevated or borderline levels of acquired risk factors, namely elevated blood pressure, overweight/obesity, diabetes mellitus, smoking, and prior cardiac disease (RR Huxley, et al., 2011). Thus, AF would have been avoidable through improvement of cardiovascular risk factors in many cases. About 90% of the population-attributable risk of acute stroke was associated with 10 potentially modifiable cardiovascular risk factors (INTERSTROKE project, MJ O´Donnell, et al., 2016). The ARIC Study also showed that the cumulative probability of incident AF increased with increasing numbers of the components of the Metabolic Syndrome (AM Chamberlain, et al., 2010).

In contrast, AF without comorbidities is rare with a prevalence of only 1.7% (E-J Kim, et al., 2016). All-cause mortality and total cardiovascular events were highest in "Typical AF", lowest in "Non-AF" and intermediate in „AF no comorbidity" subgroups.

The association of excessive sports with the prevalence and incidence of AF was reported early on by the group from Barcelona (L Mont, et al., 2002, 2009). Similar associations were later reported for long-distance ski runners (J Grimsmo, et al., 2010)

PROGNOSIS OF PATIENTS WITH ATRIAL FIBRILLATION

Patients with AF have an increased mortality and morbidity. The increase in mortality may be a consequence of AF, of therapeutic measures or of underlying conditions. Even short (>190/min, duration >6 min) atrial high rate episodes detected

in pacemaker memories are associated with an increased incidence of stroke and systemic embolism (JS Healey, 2012; L Friberg, et al., 2007; OD Pedersen, et al., 2006; M Rivero-Ayerza, et al., 2008; TV Glotzer, et al., 2003). Therefore, AF justifies intensified therapy of comorbidities. Early diagnosis of AF before complications (stroke, death) occur is needed.

ASSOCIATION BETWEEN ATRIAL FIBRILLATION AND STROKE

In the presence of AF, early data from the Framingham Study showed that in patients without rheumatic heart disease, the risk of stroke was more than 5-fold increased, in those with rheumatic heart disease even 17-fold (Ph A Wolf, et al., 1978). The authors hypthesized from their data that deaths and consequences of stroke might be preventable by restoration of sinus rhythm or by prevention of left atrial thrombi using long-term anticoagulation in patients without rheumatic heart disease. Whereas the latter was proven to be true by subsequent trials on stroke prevention in AF, the first one has still not yet been clearly proven.

Recent data have shown that between 31% (Hannon N, et al., 2010) to 33% of strokes were associated with AF (Friberg L, et al., 2014).

In the 1990-ies, randomized landmark trials on stroke prevention in AF (SPAF) have clearly shown that the risk of stroke can be reduced by about two thirds by oral anticoagulation with vitamin K-antagonists (V Fuster, et al. 2006; RG Hart, et al., 1999). During recent 10 years, four novel direct acting factor II or Xa antagonists (non-vitamin K-antagonists such as dabigatran, rivaroxaban, apixaban and edoxaban) have been introduced based on large randomized trials. They have been shown to be at least as effective as warfarin but have less serious intracranial bleeding (one of many reviews, see: A Lowenstern, et al., 2018).

SYMPTOMS ASSOCIATED WITH ATRIAL FIBRILLATION

Symptoms include palpitation, dizziness, rarely syncope, dyspnea, reduced exercise capacity, angina-like symptoms, anxiety but in two of three episodes of AF, patients have no symptoms (T Fetsch, et al., 2004).

The course of disease in atrial fibrillation is complex and seems erratic (P Kirchhof, et al. 2007). The standard scheme of progression of AF from first diagnosis to episodes of paroxysmal, then persistent and permanent AF is often not followed since episodes may remain paroxysmal for many years or forever, or AF may manifest itself from the onset as persistent or permanent. In the prospective long-term registry of the German Atrial Fibrillation NETwork (AFNET), we found no difference in the survival rates among patients with AF and different presenting patterns, from first episode to permanent AF, also suggesting that the above classical categories are not very helpful for prognostication (M Näbauer, et al., in preparation). In contrast, in patients with nonvalvular AF referred for electrical cardioversion, persistent AF compared with paroxysmal AF was independently associated with increased mortality (M Leung, et al., 2017).

Due to the variability of the course of AF, there is a renewed interest in its better categorization. The association of AF clinical phenotypes with treatment patterns and outcomes was assessed by cluster analyses in the multicenter registry ORBIT-AF (T Inohara, et al., 2018). Four clinically relevant phenotypes of AF were identified, each with distinct associations with clinical outcomes, underscoring the heterogeneity of AF and the importance of comorbidities and substrates. These four groups were those with (1) low comorbidity, (2) younger behavioral (lifestyle) disorders, (3) tachy-bradyarrhythmias and device implantation, and (4) atherosclerotic co-morbidity, with increasing mortality in the sequence from (1) to (4).

ATRIAL FIBRILLATION IS A PROGRESSIVE DISEASE WITH COMPLEX PATHOPHYSIOLOGY

The complex pathophysiological mechanisms that lead to AF include electrophysiological changes, occurrence of triggering factors, hemodynamic and structural changes (U Schotten, et al., 2011). Whereas early on, the emphasis of research was on the electrophysiological mechanisms, further work has more and more dissected the role of inflammation and fibrosis. It could be shown that human epicardial adipose tissue but not subcutaneous adipose tissue, induces fibrosis of the atrial myocardium in an organo-culture model of rat atria. The extent and biological activity of epicardial adipose tissue is associated with AF and depend on clinical conditions (diabetes mellitus type II, metabolic syndrome, obesity, obstructive sleep apnea, ischemic heart disease, heart failure or ageing) (N Venteclef, et al., 2015).

Obesity results in progressive atrial structural and electrical remodeling. In a sheep model, obesity was associated with atrial electro-structural remodeling, leading to increases in atrial size, decrease of conduction velocity, increases in fibrosis and of expression of profibrotic mediators. These changes were associated with spontaneous and more persistent AF (HS Abed, et al., 2013). In line with these experimental findings, the volume of pericardial fat in patients was significantly associated with presence of AF, with AF chronicity, AF symptom burden, left atrial volume, and long-term AF recurrence after catheter ablation (Ch X Wong, et al., 2011).

Imaging of atrial fibrosis plays an increasing role. The extent and pattern of atrial tissue fibrosis identified by delayed enhancement MRI was a strong predictor of the likelihood of arrhythmia recurrence after AF catheter ablation (NF Marrouche, et al., 2014).

HOW DOES PERSONALIZED MEDICINE FOR A PATIENT WITH AF LOOK LIKE TODAY?

Tailoring of treatment to symptoms, diagnosis, and prognosis of the individual patient has always been the goal of patient management. Only more recently, the term “personalised medicine” has increasingly been used based on the hope that the growth of new diagnostic and therapeutic modalities will enable a more personalised approach.

Only rarely may a simple look at the ECG provide a wealth of information as in case of interatrial block that was first described by Antoni Bayés de Luna, et al. (1985; 1988). This characteristic +/- P-wave pattern and its clinical spectrum is nowadays referred to as the Bayes syndrome (A Bayes de Luna, et al., 2012). These are usually elderly patients who have a high propensity of AF and stroke where a detailed search for AF should be done, then requiring oral anticoagulation.

Standard management of patients with AF includes optimal medical therapy of underlying comorbidities, prevention of thromboembolism (stroke, TIA, systemic emboli), improvement of symptoms, rate (av-node slowing during AF) and rhythm control (termination of AF; stabilization of sinus rhythm by drugs or ablation). In the majority of patients, this present ”classical“ approach is informed by scoring systems for symptoms, for risk of stroke and systemic embolism, and for bleeding to decide on these various categories of management. However, these scores do not take into account the complex pathophysiology of AF. In addition, these scores although used in clinical practice and endorsed by current AF guidelines, have major limitations. While they are helpful when comparing subgroups of patients, they are less helpful when used for management decisions in individual cases. For instance, the EHRA score for symptoms (P Kirchhof, et al., 2007) and the $CHADS_2$ score (BF Gage et al., 2001) and the CHA_2DS_2-VASc score for predicting the risk of stroke and systemic embolism have proven useful in clinical practice and are recommended tools by current guidelines. In reality, they suffer from imprecise definition of their components (e.g. different severities and durations of hypertension or diabetes mellitus are lumped in one score point each). The variation of risk within a score category overlaps with higher and lower

score points. Despite these limitations, they are frequently used tools in clinical practice but they are far from a strictly tailored application to the individual case.

Therefore, further improvements in management of AF patients are likely to require a personalised management targeted at individual pathophysiology, clinical risk, and predisposition (P Kirchhof, et al., 2013). Such a personalised AF management approach would require careful case-by-case assessment of the causes and consequences of AF, based on information which should be collected through history taking, improved risk scores, the electrocardiogram, imaging of heart and brain, and analysis of blood and DNA (P Kirchhof, et al., 2013). Figure 1 shows the complexity of interactions of parameters and techniques available but not yet fully exploited.

Since scores are based on group comparisons and have limited association with individual patients, it is difficult to give answers to the following and other questions: Who specifically is going to suffer a stroke? Who is not going to suffer a stroke? What is the role of other than the conventional risk markers or factors? What is the impact of biomarkers, genetics, and genomics or proteomics? How to adequately manage comorbidities? How to better consider the complexity of decision trees? Thus, we are still far from a truly personalised approach. With regard to the complex pathophysiology and course of AF, this may even be very difficult to achieve in the near future.

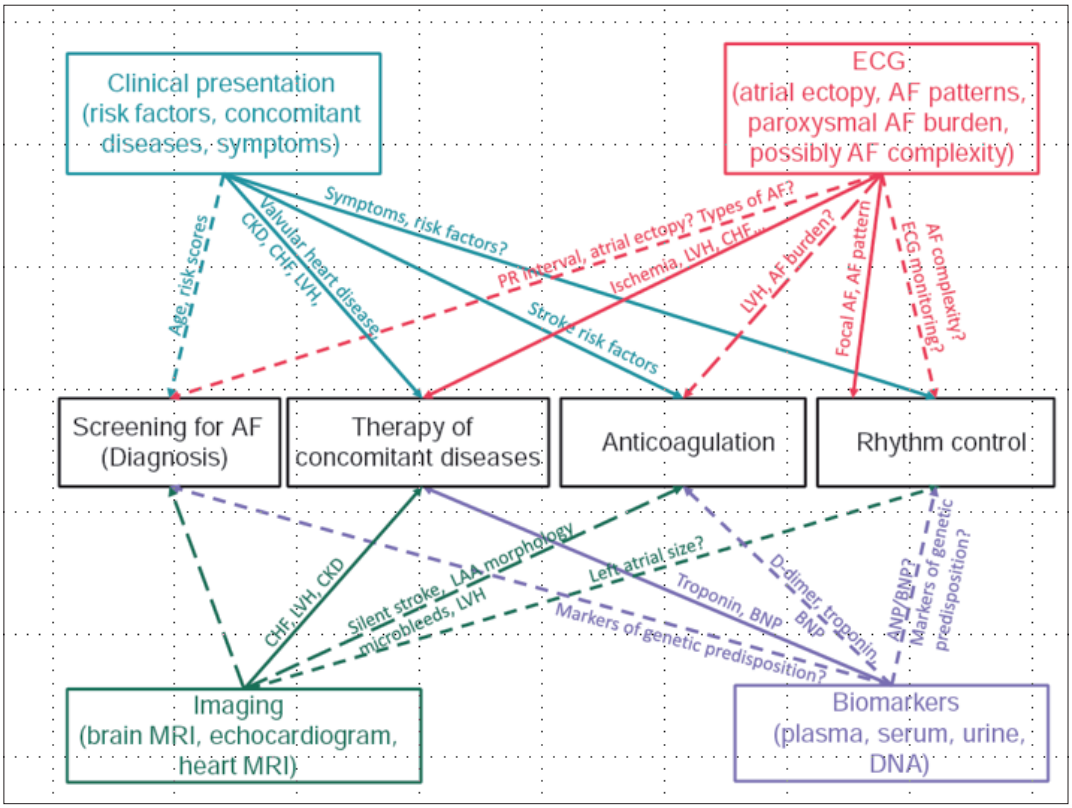

Figure 1: Types of information that may be used to personalise AF management (From: P Kirchhof, G Breithardt, et al., 2013, *permission to reproduce under the terms of the Creative Commons CC BY license*).

ARTIFICIAL INTELLIGENCE AND BIG DATA – THE SOLUTION FOR A MORE PERSONALISED MANAGEMENT OF PATIENTS WITH ATRIAL FIBRILLATION?

There is hope that our ignorance may subside with more and better information on AF as a complex disease, derived from Big Data analyses using Artificial Intelligence (AI). Such analyses should be based on a multitude of available and coming data ranging from clinical parameters that go beyond the standard clinical characteristics, to biomarkers, genomics and proteomics, and high resolution electrocardiograms and imaging techniques.

One can find many definitions of AI. One that I like most is "Artificial Intelligence is the ability of a non-natural entity to make choices by an evaluation process" as suggested by Jacob Turner (2019). The European Commission's Communication on AI defines it in the following way "Artificial intelligence (AI) refers to systems that display intelligent behaviour by analysing their environment and taking actions – with some degree of autonomy – to achieve specific goals" (2018).

Whereas conventional networks fix the architecture before training starts, artificial neural networks use weights in order to determine the connectivity between inputs and outputs (S Han, et al., 2015). In machine learning systems, the weights can be re-calibrated by the system over time, often using a process called back-propagation, in order to optimise outcomes (DE Rumelhart, et al., 1986).

Presently, there are three types of techniques that are summarized as AI (C Krittanawong, et al., 2017). *Machine Learning* may build automated clinical decision systems to make more accurate predictions, rather than simple estimated score systems. *Deep Learning* mimics the operation of the human brain. It uses multiple layers of artificial neuronal networks, and is, for instance, very powerful in image recognition. *Cognitive Computing* involves self-learning systems using machine learning, pattern recognition, and natural language processing with the goal to create automated computerized models that can solve problems without human assistance.

Access to large health data sets and the use of AI may open new opportunities for clinical and translational research into AF. This may result in the discovery of new mechanisms, and in improvement of the quality of care. Development of prediction models has become an important tool for subclassification of patients but only few studies exist in AF (JAAG Damen, et al., 2016). The most relevant advantage of machine learning algorithms lies in their ability to identify unforeseen classifiers for disease states. Unsupervised data analysis techniques alone or in combination with more traditional methods, have seen an increase in use for AF research, e.g. for identification of patients with AF.

Our own experience with Neural Networks goes back to the late 1990-ies when we analyzed clinical data from coronary interventions within a multicenter project. This clearly showed the potential of Neural Networks to come to important conclusions (Th Budde, et al., 1997, 1999). Recently, G-P Diller from our institution, jointly with other groups from London and Zagreb as well as with the Competence Network for Congenital Heart Defects, could demonstrate the potential utility of machine learning algorithms trained on large datasets to estimate prognosis and to guide therapy in patients with congenital heart disease (G-P Diller, et al., 2019a). In another recent study (G-P Diller, et al., 2019b), the potential of machine learning algorithms, trained on routine echocardiographic datasets, to detect underlying diagnosis in complex congenital heart disease, could be demonstrated.

Risk prediction has been refined using automated analysis of extensive routine clinical data like ECG analysis (ZI Attia, et al.,2019a, b). In a retrospective analysis, an AI-based ECG algorithm using a convoluted neural network, successfully identified patients with AF with high sensitivity and specificity when in sinus rhythm at the time of ECG recording (ZI Attia, et al., 2019a). In another study from the same institution, paired 12-lead digitized ECGs from 44,959 patients at Mayo Clinic were

used to screen for cardiac contractile dysfunction as assessed by echocardiography using a testing and a validation set of patients. The ECG was able to predict the long-term incidence of developing an EF of ≤35% even if left ventricular function was still considered as normal at the time of initial evaluation (ZI Attia, et al., 2019b).

While these examples are not from the field of atrial fibrillation, they serve to demonstrate first, that AI in its broadest sense is not a new technique but an evolving one, and second, to show the applicability of machine and deep learning techniques.

A project in which our AFNET has been involved, is "Characterizing Atrial fibrillation by Translating its Causes into Health Modifiers in the Elderly" (CATCH ME) under EU Horizon 2020. Its aim has been to identify the major health modifiers causing AF in the elderly in Europe, to develop clinical tools that will personalise the prevention and management of AF patients, and to guide and strengthen future strategies to prevent, diagnose, and treat AF in Europe (http://www.catch-me.info/). This project includes among its multinational members from UK, Germany and the Netherlands, also the Institut d'Investigacions Biomédiques August Pi i Sunyer (IDIBAPS) of Barcelona, represented by two investigators, Lluís Mont and Eduard Guasch.

The CATCH ME consortium recently reported the results of a data-driven discovery and validation of circulating blood-based biomarkers associated with prevalent AF using regression and machine learning (W Chua, et al., 2019). The forward selection process identified 3 clinical risk factors and 3 biomarkers that were significantly associated with AF: age, sex, body-mass-index (BMI), BNP, FGF23, and TrailR2. Among the biomarkers, Brain Natriuretic Peptide and Fibroblast Growth Factor 23 were identified by both techniques, regression and machine learning. They were robustly associated with AF in this cohort of 638 patients presenting to hospital (W Chua, et al., 2019). From studies that used conventional statistical analyses, it is apparent that further information can be obtained from biomarkers and genetic markers that may help in personalised decision-making. For instance, a combination of circulating type I collagen-related biomarkers was associated with AF (S Ravassa, et al., 2019). The Framingham Heart Study showed that the estimation of polygenic AF risk is feasible and together with clinical risk factor burden explains a substantial gradient in long-term AF risk (LC Weng, et al., 2018).

These examples demonstrate the potential of AI and suggest a strong future expanding role for AI also in AF. Like AF, other cardiovascular diseases are complex and heterogenous in nature as well, caused by multiple genetic, environmental, and behavioral factors. Rather than assessing a simple score system or traditional cardiovascular risk factors, outcomes need to be predicted more accurately and effectively. The paradigm is shifting from traditional statistical tools to the use of AI in cardiovascular medicine to enable precision cardiovascular medicine. Rather than replacing physicians, AI will assist in making better clinical decision (Ch Krittanawong, et al., 2017).

What is the present role of AI? There has been much hope and hype about it. We need critical analyses to assess the performance of AI in comparison to standard statistical approaches like the systematic review by E Christodoulou, et al. (2019). Machine learning models do not automatically lead to improved performance over traditional methods. The feasibility of using electronic health record data for predicting incident atrial fibrillation was just recently shown. However, this model did not perform substantially better than a logistic regression model with standard risk factors (P Tiwari, et al., 2020). Model validation procedures are often not sound or not well reported which hampers a fair model comparison in real-world case studies (E Christodoulou et al., 2019). Research should focus more on identifying which algorithms have optimal performance for different types of prediction problems (E Christodoulou, et al., 2019). Models that have self-learning capacity will deviate from their original (approved) version over time which

means that the originally approved version does no longer exist (TJ Hwang, et al., 2019).

ADDRESSING ETHICAL CHALLENGES

E. Vayena, et al. (2018) have addressed immanent ethical issues for machine learning in medicine. They claim that data sourcing must adhere to data protection and privacy requirements. Its development should be committed to fairness. Poorly representative training data sets can introduce biases into machine learning-trained algorithms. Data sources must reflect true epidemiology within a given demographic. The data set must contain enough members of a given demographic. The deployment of machine learning should satisfy transparency standards. The inner logic of noninterpretable, so-called black box algorithms may remain hidden even to their developers. For machine learning to be ethical, developers must communicate to their end users - doctors - the general logic behind machine learning-based decisions.

The European Union (EU) has established an EU High Level expert Group on Artificial Intelligence. This useful document was made public in April 2019. Within the ongoing consultation process, the European Society of Cardiology has responded on time.

On a global scale, A. Jobin, et al. (2019) found an agreement that AI should be 'ethical' but what constitutes 'ethical Artificial Intelligence' was a matter of debate. Five ethical principles (transparency, justice and fairness, non-maleficence, responsibility and privacy) appeared with substantial differences in interpretation, importance, applicability, and implementation.

There are many more issues which are addressed in the book by Jacob Turner (2019). This includes questions like whether robots should have rights, whether robots may have feelings and a legal personality, whether we need changes to some fundamental legal concepts, what is the liability of robots in criminal law, and in negligence, product liability, vicarious liability, contract, insurance and intellectual property in civil law.

In a very recent interview, Christian Johner (Physician and founder/owner of the Johner Institut GmbH) (https://healthcare-in-europe.com/en/news/ai-hype-hope-reality.html) addressed some important issues. He said that there is already a shortage of physicians and healthcare will not become easier in the future. His hope was that AI will ease physicians' workload – after all, these systems are programmed to support them in routine tasks. In some areas, AI is more powerful than the human brain, but that is not a new experience. He mentioned that a truck is better at transporting things than a human. That is how we should look at AI: it is a tool that can perform certain tasks better than we humans. AI will give physicians more time to actually deal with patients.

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